CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-278

STATISTICAL REVIEW(S)

Statistical Review & Evaluation

NDA #:	21-278
Sponsor:	Celgene Corporation
Drug Name:	Methylphenidate HCl (Attenade)
Indication:	ADHD
Date received:	October 25, 2000
Medical officer:	Dr. Roberta Glass
Biometrics reviewer:	Kallappa M. Koti

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1. OVERVIEW

[redacted] These will accommodate the recommended doses: 5 to 20 mg/day (2.5 to mg/day given twice daily, b.i.d.). *d*-methylphenidate hydrochloride (*d*-MPH) is the *threo*-enantiomer of racemic methylphenidate (most commonly known by trade name Ritalin®).

Following an evaluation of the potential benefits and value of *d*-MPH as a therapy for ADHD, Celgene prepared and submitted an Investigational New Drug application (IND [redacted] in 1996. Six hundred eighty-four unique children with ADHD have been exposed to *d*-MPH in six Celgene sponsored studies and an additional 15 healthy adult volunteers have participated in a pharmacokinetic study. The phramacokinetic profile of *d*-MPH is similar regardless of whether it is given as *d*-MPH or the racemic mixture, *d,l*-MPH. Therefore, the safe use of racemic methylphenidate for more than 40 years provides additional support for the safe use of *d*-MPH. A letter of authorization of NDA 10-187 for Ritalin® has been provided by Novartis Pharmaceutical Corporation and is included in this New Drug Application.

Three clinical studies analyzing the in vivo pharmacokinetic of *d*-MPH have been conducted. Two of the studies conducted in children diagnosed with ADHD between the ages of 6 and 16 years, Studies 970M-01 and *d*-MPH-PK-99-001, and a third study examined the effects of food on *d*-MPH pharmacokinetics in healthy adult volunteers, Study *d*-MPH-PK-00-001. Results are similar to those reported in the published literature.

Two adequate and well-controlled studies of *d*-MPH have been conducted in patients with ADHD, Study **97-M-02**, a placebo- and active (*d,l*-MPH)-controlled, parallel group, 4-week study and Study **97-M-03**, a double blind, placebo-controlled, 2-week, withdrawal study. The majority of patients participating in these two trials, 180 of 241 patients, have continued to receive *d*-MPH in long-term, open label, extension studies. An additional 453 patients have enrolled directly into one of two open label safety studies, Study 970-M-04 and Study 97-M-05. Four hundred twenty-six patients have continued to receive *d*-MPH for 6 months or more, and 146 completed 1 year of treatment. Other than one published pharmacokinetic study, Celgene is not aware of any other clinical source of safety information for *d*-MPH.

An overview of the study design, demographics and dosing of these studies is presented in Table 1.1 on the next page. An overview of schedule of events is presented in Table 1.2 on the next page.

Table 1.1

Celgene-sponsored Randomized Controlled Studies Conducted in Children with ADHD

Study No.	Design	N Male/Female	Ethnicity/ Country	Mean Age (Years) [range]	Dosing (mg/day)
97-M-02	Randomized, Double-blind, Placebo- and Active controlled	116 males 16 females	103 Caucasians 18 African-Am. 4 Hispanic 7 Other	9.8 [6 to 17]	*d*-MPH 5 to 20 mg/day; *d,l*-MPH 10 to 40 mg/day or matching placebo
97-M-03	Randomized, Double-blind, placebo-controlled withdrawal	72 males 17 females	68 Caucasian 13 African-Am. 8 Hispanic	10 [6 to 16]	*d*-MPH 5 to 20 mg/day or matching placebo

Table 1.2

Overview of Efficacy Procedure in the Double-blind Studies

Study 97-M-02	1-week Single Blind Placebo (Visits 2-3)	**4-week Double Blind Treatment**				
		Baseline (Visit 3)	Week 1 (Visit 4)	Week 2 (Visit 5)	Week 3 (Visit 6)	Week 4 (Visit 7)
Study 97-M-03	6-week Open Label d-MPH (Visits 2-8)	2-week Double-blind Withdrawal				
		Baseline (Visit 8)	Week 1 (Visit 9)	Week 2 (Visit 10)		
Study Procedure						
Teacher-SNAP-ADHD		X[1]	X[1]	X[1]	X[1]	X[1]
Parent-SNAP-ADHD		X[2]	X[2]	X[2]	X[2]	X[2]
CGI-I		X[3]	X	X	X	X
CGI-S	X	X[3]				
Math Test (Home)		X[2]	X	X	X	X
Math Test (Clinic)		X[3]	X	X	X	X
Study Medication	X	X	X	X	X	
Study Termination						X

[1] To be recorded weekly by the teacher at school in the afternoon, during the work preceding the listed clinic visit.

[2] SNAP-ADHD to be recorded twice daily on the weekends by the parent and any day the child was not in school, and the Math Test once daily during the week preceding the clinic visit.

[3] To be evaluated prior to dispensing double-blind medication.

2. STUDY 97-M-02

The primary objective of this protocol was to determine the comparative efficacy of twice daily doses of *d*-MPH versus placebo in reducing symptoms of ADHD in children.

This was a double-blind, randomized, placebo-controlled trial that is preceded by a 1 week single-blind, placebo, run-in phase testing the effects of *d*-MPH and *dl*-MPH in children with ADHD.

After screening for eligibility, all children will receive placebo in a single-blind fashion to assess the symptoms of ADHD when no active medication is given. This phase is also used to disqualify children who demonstrate a therapeutic response to placebo. A Therapeutic Response is defined as a score of either 1 (Very much improved) or 2 (Much improved) on the investigator's Clinical Global Impression-Improvement scale (CGI-I).

During the double-blind phase, children will be randomized to 1 of 3 treatment groups. One group will receive twice daily dosing of *d*-MPH, starting at 2.5 mg and increasing, as necessary, to 10 mg; a second group will receive twice daily dosing of *dl*-MPH, starting at 5 mg and increasing, as necessary, to 20 mg; a third group will receive twice daily dosing of placebo. The first dose of study medication will be given between 7 and 8 AM, and the second dose will be given between 11:30 AM and 12:30 PM. The duration of each child's participation in this phase is 4 weeks.

> During the first week of the double-blind phase, children randomized to *d*-MPH will receive 2.5 mg, twice daily; children randomized to *dl*-MPH will receive 5 mg, twice daily; and children randomized to placebo will receive placebo twice daily. If a therapeutic response (compared to the Baseline Visit, i.e., Visit 3) is noted, then that dose of study medication will be maintained for 3 weeks (4 weeks total).
>
> If a therapeutic response is not observed after the first week of treatment, then children randomized to *d*-MPH will have their dose increased to 5 mg, twice daily; children randomized to *dl*-MPH will have their dose increased to 10 mg, twice daily; and children randomized to placebo will be given that study medication twice daily. If a therapeutic response is observed, then that dose of study medication will be maintained for 2 additional weeks (3 weeks total).
>
> If a therapeutic response is not observed after the second week of treatment, then children randomized to *d*-MPH will have their dose increased to 10 mg, twice daily; children randomized to *dl*-MPH will have their dose increased to 20 mg, twice daily; and children randomized to placebo will be given that study medication twice daily. The children will be treated with this dosage regimen for 2 weeks.

The study duration is for 6 weeks. A total of 132 children were recruited in 11 centers. These boys and girls were 6-17 years of age. The study flow chart is shown in Table 2.1 below.

Table 2.1
97-M-02 Study Flow Chart

Events	Visit						
	1	2	3	4	5	6	7
Medical / Physical	X						X
Conc. Meds.	X						X
T-SNAP-ADHD (2)		X	X	X	X	X	X
P-SNAP-ADHD (4)		X	X	X	X	X	X
CGI-I		X	X	X	X	X	X
CGI-S		X	X				
Math Test		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Study Medication		X	X	X	X	X	

Several efficacy measures are used in this trial. A few important measures are: the SNAP-ADHD Scale, the investigator's CGI-I, the investigator's Clinical Global Impression-Severity of Illness scale (CGI-S), the Percent of Therapeutic Responders, and a Math Test.

The SNAP-ADHD Rating Scale, an abbreviated version of SNAP-IV Rating Scale developed by groups directed by [redacted] consists of 18 questions:

1. *Often fails to give close attention to details or makes careless mistakes in schoolwork or tasks.*
2. *Often has difficulty sustaining attention to tasks or play activities.*
3. *Often does not seem to listen when spoken to directly.*
4. *Often does not follow through on instructions and fails to finish schoolwork, chores, or duties.*
5. *Often has difficulty organizing tasks and activities.*
6. *Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort.*
7. *Often loses things necessary for activities (e.g., toys, school assignments, pencils, or books).*
8. *Often is distracted by extraneous stimuli.*
9. *Often is forgetful in daily activities.*
10. *Often fidgets with hands or feet or squirms in seat.*
11. *Often leaves seat in classroom or in other situations in which remaining seated is expected.*
12. *Often runs about or climbs excessively in situations in which it is inappropriate.*
13. *Often has difficulty playing or engaging in leisure activities quitly.*
14. *Often is "on the go" or often acts as if "driven by a motor".*
15. *Often talks excessively.*
16. *Often blurts out answers before questions have been completed.*
17. *Often has difficulty awaiting.*
18. *Often interrupts or intrudes on others (e.g., butts into conversations/games).*

Either the teacher or the parent is asked to indicate, for each question, which of the following four choices best describes the child: Not at ALL, Just A Little, Quite A Bit, or Very Much. The rating is based on a 0 to 3 scale: Not at ALL = 0, Just A Little = 1, Quite A Bit = 2, and Very Much = 3. The score for SNAP-ADHD is the average rating per item that is calculated by summing the scores on all 18 items and dividing by 18. Teachers at the end of the school day will complete the SNAP-ADHD Rating Scale, twice weekly

during the school week. *An average score below "1" is an indicates behavior that is well controlled.* **The primary efficacy measure is the change in the Teacher SNAP-ADHD scores between Visit 3 and Visit 7.** The null hypothesis H_0: The mean change from Visit 3 to Visit 7 in Teacher SNAP-ADHD score for the *d*-MPH group is the same as that of the placebo group. An analysis of covariance model accounting for treatment, site, and any baseline covariates will be used.

The child's CGI-I score at the final visit (Visit 7) is used as a secondary measure of efficacy. Similarly, the percent of Therapeutic Responders, determined at Visit 7 for the *d*-MPH, *dl*-MPH and placebo groups, is used as a secondary measure of efficacy. The percent of patients responding to treatment at the end of the double-blind phase will be compared using the Mantel-Haenszel Test adjusting for investigators.

3. STUDY 97-M-03

The primary objective of this protocol was to determine the comparative efficacy of *d*-MPH relative to placebo in maintaining a reduction of ADHD symptoms in children who are responding to *d*-MPH. A secondary objective is to determine the duration of efficacy of *d*-MPH.

This study starts with a 4 to 7 day screening period. The study has 3 parts: Part A is a 6-week, open-label titration and treatment phase in which all children will receive *d*-MPH. Children will be titrated to an efficacious dose of *d*-MPH within first 4 weeks, and then maintained on that dose *d*-MPH for the remainder of Part A. Part B is a double-blind, randomized, placebo-controlled, withdrawal phase of 2 weeks in duration. Part C is an open-label treatment phase of 18 weeks in duration in which all children will receive *d*-MPH. In Part B, children will be randomized, in a double-blind fashion, into two groups. One group will receive *d*-MPH, twice daily, at the same dose as they had received during the final 2 weeks of Part A. The other group will receive a matching placebo, twice daily. A total of **87** boys and girls of 6-17 years were enrolled- over **7** centers. The study flow chart is shown in Table 3.1 below.

Table 3.1
97-M-03 Study Flow Chart

Study Phase	**Part A Open Label**			**Part B Withdrawal**	**Part C Open Label**
Week	**Scrn**	**Week 1 to 6**		**Week 7 to 8**	**Week 9 to 27**
Visit	1-2	3	Visit 4 to Visit 7	Visit 8 & 9	Visit 10-13
Medical/Physical	X	X		X	X
CGI-S				X	
CGI-I		X	X	X	
Teacher SNAP-ADHD		X	X	X	
Parent SNAP-ADHD		X	X	X	
Math Test				X	
Study medication		X	X	X	X

The percent of Treatment Failures, determined at the last visit of the withdrawal phase (Visit 10 or Visit 9 if the patient discontinues the withdrawal phase after Visit 9), will be used as the **primary efficacy measure** and compared between the 2 groups. A Treatment Failure is defined as a score of either 7 (Very much worse) or 6 (Much worse) on the investigator's CGI-I during the withdrawal phase, relative to Visit 8. The treatment groups will be compared using the Mantel-Haenszel Test adjusted for sites.

The **change** in the Teacher SNAP-ADHD scores between the final visit of the withdrawal phase (Visit 9 or Visit 10) and Visit 8 is a secondary efficacy variable. The *d*-MPH and the placebo groups will be compared using an ANOVA model accounting for treatment, investigator, and treatment by investigator interaction. Baseline measurements for the treatment groups in Part B are those obtained at Visit 8.

4. SPONSOR'S EFFICACY RESULTS

In Study 97-M-02, the average improvement from baseline on the Teacher SNAP-ADHD (the primary efficacy measure) for both the *d*-MPH and *d,l*-MPH treatment groups (-0.7) was equivalent to one standard deviation at baseline and reflects strong clinical improvement; in comparison, the mean change from baseline for placebo-treated patients was smaller (-0.2) indicating a lack of improvement in this group. The change was statistically significantly greater in the *d*-MPH group than in the placebo group when using data from those patients who completed the 4 weeks ($p=0.0004$) and also when using the last available rating (LOCF) for all patients ($p<0.0001$). Similarly, statistically significant difference were found between the *d,l*-MPH group and the placebo group ($p=0.0042$ for the observed cases and $p=0.0015$ for the LOCF sample).

The sponsor's results on Teacher SNAP-ADHD at baseline and the final visit are reproduced in Table 4.1 below.

In Study 97-M-02, the percentage of patients who were considered Therapeutic Responders at the end of the double-blind period (Visit 7) is presented in Table 4.2 below.

In Study 97-M-03, the primary efficacy measure 'Treatment Failure' was defined as a CGI-I score of either "much worse" or "very much worse". At the end of the 2-week double-blind withdrawal (Visit 10), 6 of 35 patients (17.1%) randomized to *d*-MPH and 24 of 39 patients (61.5%) randomized to placebo were considered treatment failures. This difference was statistically significant ($p=0.001$). A summary of these is shown in Table 4.2 below.

Table 4.1

Teacher SNAP-ADHD at Baseline and Final Visit of double-blind treatment

	Study 97-M-02 (Double-blind)			Study 97-M-03 (open-label)
	d-MPH	*d,l*-MPH	Placebo	*d*-MPH
Baseline (Visit 3)				
N	42	41	41	77
Mean ± SD	1.4± 0.7	1.8± 0.7	1.6± 0.7	1.4± 0.8
Range	[redacted]			
Final Visit [1]				
N	39	37	36	63
Mean ± SD	0.8 ±0.7	0.9± 0.8	1.4± 0.8	0.7± 0.7
Range	[redacted]			

	Double-blind	
Baseline	***d*-MPH**	**Placebo**
N	28	35
Mean ± SD	0.7± 0.7	0.7± 0.7
Range	[redacted]	
Week 2 (Visit 10)		
N	27	32
Mean ± SD	0.7 ±0.7	1.4± 0.9
Range	[redacted]	

[1] Final visits were Visit 7 (4 weeks of treatment) for study 97-M-02 and Visit 8 (6 weeks of treatment) for Study 97-M-03.

Table 4.2

Proportion of Therapeutic Responders (CGI-I Scores) and Treatment Failures

	Study 97-M-02 End of Double-blind Treatment (4 Weeks)			Study 97-M-03 End of Open-label TRT (6 weeks)	
Response Category*	***d*-MPH**	***d,l*-MPH**	**Placebo**	***d*-MPH**	**Placebo**
N	44	46	41	34	40
Responders	29 (65.9%)	22 (48.9%)	8 (19.5%)	33 (97.1%)	40 (100%)
Non-Responders	15 (34.1%)	23 (51.1%)	33 (80.5%)	1 (2.9%)	0
				End of Double-blind Withdrawal (2 Weeks)	
N				35	40
Therapeutic failure				6 (17.1%)	25 (62.5%)
Non-failure				29 (82.9%)	15 (38.5%)

* A responder is a patient with a CGI-I score of "very much improved" (1) or "much improved" (2); non-responders are those patients with CGI-I scores of 3 to 7. For Study 97-M-03, a therapeutic failure is a patient with a CGI-I score of "much worse" (6) or "very much worse" 97).

The results of the ANCOVA analysis for the primary efficacy variable of Study 97-M-02 as presented by the sponsor are shown in Table 4.3 below. The test score at baseline was the covariate, and treatment, site, and the site by the treatment interaction are included in the model.

Table 4.3
Analysis of Teacher SNAP-ADHD Score- Change from Baseline (Visit 3)
After 4 Weeks of Double-blind Treatment (Visit 7)
Study 97-M-02

Average Test Score	d-MPH N=44	d,l-MPH N=46	Placebo N=42	p-value d-MPH vs Placebo	p-value d,l-MPH vs Placebo	p-value d-MPH vs d,l-MPH
Observed Cases						
N	38	33	35			
Mean ± SD	–0.7± 0.7	–0.7 ±0.6	–0.3 ±0.7	0.0004	0.0042	0.6107
Median	-0.6	–0.8	–0.2			
Range	[redacted]					
95% C.I.	(-1.0, -0.5)	(-1.0, -0.5)	(-0.5, -0.1)			
Last Observation Carried Forward (LOCF)						
N	42	38	39			
Mean ± SD	-0.7 ± 0.7	-0.7 ± 0.7	-0.2 ± 0.7	<0.0001	0.0015	0.4197
Median	-0.5	-0.7	-0.2			
Range	[redacted]					
955 C.I.	(-0.9, -0.5)	(-0.9, -0.4)	(-0.5, 0.0)			

Source: Page 38, volume 1.118

5. REVIEWER'S ANALYSES

Summary of Baseline Demographics by Treatment Group is as follows.

Table 5.1: Demographics

Baseline Characteristic	Study 97-M-02			Study 97-M-03	
	d-MPH	*d,l*-MPH	Placebo	*d*-MPH	Placebo
Age (years)					
Mean ± SD	10.0 ± 2.5	9.8 ± 2.8	9.6 ± 2.7	10.1± 2.9	9.9± 2.7
Median	9.5	9.0	9.0	10	9.5
Range	6 – 16	6 – 17	6 - 16	6 – 16	6 - 16
Sex n (%)					
Male	41 (93.2)	40 (87.0)	35 (83.3)	5 (14.3)	9 (22.5)
Female	3 (6.8)	6 (13.0)	7 (16.7)	30 (85.7)	31 (77.5)
Ethnicity n (%)					
Caucasian	35 (79.5)	34 (73.9)	34 (81.0)	28 (80)	30 (75)
African American	5 (11.4)	6 (13.0)	7 (16.7)	5 (14.3)	5 (12.5)
Asian	0 (0.0)	1 (2.2)	0 (0.0)	0	0
Hispanic	2 (4.5)	1 (2.2)	1 (2.4)	0	0
Other	2 (4.5)	4 (8.7)	0 (0.0)	2 (5.7)	5 (12.5)

5.1 Study 97-M-02

The primary efficacy measure for Study 97-M-02 is the change in the Teacher SNAP-ADHD scores between Visit 3 and Visit 7. The child's CGI-I score at the final visit (Visit 7) and the percent of Therapeutic Responders determined at Visit 7 are secondary efficacy measures.

One-way analysis on Baseline Teacher SNAP-ADHD gives a p-value of 0.0674. However, pair-wise comparison indicates that the mean responses for d-MPH, 2.5-10mg and dl-MPH, 5-20mg are significantly different (p-value = 0.0207). The observed means and an overall summary of Teacher SNAP-ADHD are as follows.

Table 5.1.1: Teacher SNAP-ADHD
Baseline and Double-blind Treatment Phase Summary Statistics

	Study 97-M-02		
	d-MPH	*d,l*-MPH	Placebo
Baseline			
N	42	41	41
Mean ± SD	1.41± 0.73	1.78 ±0.72	1.614± 0.68
Range			
Final Visit			
N	43	43	40
Mean ± SD	0.77± 0.66	1.11± 0.89	1.46 ±0.77
Range			

Protocol defined Primary Efficacy Measure: Teacher SNAP-ADHD Change from Baseline (TSNAPC), as provided in the sponsor's data, is:

TSNAPC = Average Final Visit Teacher SNAP score - Average Baseline Visit Teacher SNAP score

Descriptive statistics for the protocol defined primary efficacy variable of Study 97-M-02 are presented in Table 5.1.2 below.

Table 5.1.2: Change from baseline in the final visit Teacher SNAP-ADHD
LOCF Analysis

Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	39	-0.2397	0.6893		
d-MPH, 2.5-10 mg	42	-0.6976	0.6554		
dl-MPH, 5-20 mg	38	-0.6566	0.6532		

The primary method of analysis proposed in the protocol is analysis of covariance that includes treatment, site, and any baseline as covariates. However, the sponsor claims that the efficacy results shown in Table 4.3 are based on the 2-way ANCOVA (GLM) model, where the test score at baseline is the covariate and treatment, site and their interaction are included in the model. This reviewer's results are presented in OUTPUT 5.1.1.

OUTPUT 5.1.1

General Linear Models Procedure

Dependent Variable: TSNAPC **Teacher Snap Change from Baseline**

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	36	26.31134670	0.73087074	1.98	0.0056
Error	82	30.21239279	0.36844381		
Corrected Total	118	56.52373950			

R-Square	C.V.	Root MSE	TSNAPC Mean
0.465492	-113.5731	0.6069957	-0.5344538

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TSNAPB	1	4.88810721	4.88810721	13.27	0.0005
INV_NO	11	3.75255917	0.34114174	0.93	0.5200
TLABEL	2	6.62356368	3.31178184	8.99	0.0003
INV_NO*TLABEL	22	9.64631493	0.43846886	1.19	0.2798

General Linear Models Procedure
Least Squares Means

TLABEL	TSNAPC LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
Placebo	-0.20487812	1	.	0.0001	0.0028
d-MPH, 2.5-10mg	-0.77274605	2	0.0001	.	0.4221
dl-MPH, 5-20mg	-0.65514513	3	0.0028	0.4221	.

This reviewer notes that the sponsor does not mention these results any where in the study report. For example, Table 4.3 contains the raw means- not the adjusted means shown in the above output. The sponsor has shown the standard deviation (SD) to be 0.7 which should be 0.607 (Root MSE of OUTPUT 5.1.1). Moreover, in the above analysis of covariance model, (a) the site by treatment interaction is not significant (p-value = 0.2798) and (b) the factor site is not significant (p-value = 0.52).

This reviewer considered the one-way analysis of variance on the primary efficacy variable for treatment comparison. Results of the one-way analysis of variance on the Change from Baseline in the final visit Teacher SNAP-ADHD are shown in OUTPUT 5.1.2 on the next page.

OUTPUT 5.1.2

General Linear Models Procedure

Dependent Variable: TSNAPC Teacher Snap Change from Baseline

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	5.07222489	2.53611245	5.72	0.0043
Error	116	51.45151460	0.44354754		
Corrected Total	118	56.52373950			

R-Square	C.V.	Root MSE	TSNAPC Mean
0.089736	-124.6120	0.6659936	-0.5344538

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TLABEL	2	5.07222489	2.53611245	5.72	0.0043

General Linear Models Procedure
Least Squares Means

TLABEL	TSNAPC LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
Placebo	-0.23974359	1	.	0.0025	0.0070
d-MPH, 2.5-10mg	-0.69761905	2	0.0025	.	0.7836
dl-MPH, 5-20mg	-0.65657895	3	0.0070	0.7836	.

The data provide sufficient evidence to indicate that significant difference exist among the three treatment groups (p-value = 0.0043). Each of [redacted] groups is significantly different from placebo (p-value < 0.01). However, *d*-MPH 2.5-10 mg is not significantly different from *dl*-MPH 5-20 mg (p-value = 0.7836).

The Teacher SNAP-ADHD score at the final visit under placebo, d-MPH and dl-MPH are 1.465, 0.769 and 1.106, respectively. That is, the behavior of children under d-MPH, 2.5-10 mg group is well controlled where as it is not so for other two treatment groups.

Study 97-M-02: Observed Cases data analysis- Primary efficacy Endpoint

As per the data submitted on 3/8/01, a total of 108 patients completed the study. The descriptive statistics on the primary efficacy variables are as follows.

Table 5.1.3: Change from baseline in the final visit Teacher SNAP-ADHD OC Analysis

Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	36	-0.2611	0.6982	[redacted]	
d-MPH, 2.5-10 mg	38	-0.7342	0.6724		
dl-MPH, 5-20 mg	34	-0.7426	0.6355		

The SAS output of one way analysis of variance is shown in OUTPUT 5.1.3 below.

OUTPUT 5.1.3

General Linear Models Procedure
Dependent Variable: TSNAPC Teacher Snap Change from Baseline

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	5.4638814	2.7319407	6.09	0.0032
Error	105	47.1167436	0.4487309		
Corrected Total	107	52.5806250			

R-Square	C.V.	Root MSE	CHANGE Mean
0.103914	-115.6617	0.6699	-0.5792

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TLABEL	2	5.4638814	2.7319407	6.09	0.0032

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TLABEL	2	5.4638814	2.7319407	6.09	0.0032

General Linear Models Procedure
Least Squares Means

TLABEL	TSNAPC LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
Placebo	-0.26111111	1	.	0.0030	0.0033
d-MPH, 2.5-10mg	-0.73421053	2	0.0030	.	0.9576
dl-MPH, 5-20mg	-0.74264706	3	0.0033	0.9576	.

The observed cases data provide sufficient evidence to indicate that significant difference exist among the three treatment groups (p-value = 0.0032). Each of [redacted] groups is significantly different from placebo (p-value < 0.01). However, d-MPH 2.5-10 mg is not significantly different from *dl*-MPH 5-20 mg (p-value = 0.9576).

Secondary Efficacy Measure: **Clinical Global Impression-Improvement**

A summary of CGI_I by treatment is presented in Table 5.1.4 below.

Table 5.1.4
Final Clinical Global Impression-Improvement (CGI_I) Assessment
Secondary Efficacy Measure
Study 97-M-02

	Placebo		*d*-**MPH**, 2.5 – 10mg		*dl*-**MPH**, 5-20mg	
CGI_I	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
MINIMALLY IMPROVED	10	23.8	5	11.4	4	8.7
MUCH IMPROVED	6	14.3	16	36.4	12	26.1
MUCH WORSE	1	2.4	0	0	2	4.3
NO CHANGE	16	38.1	10	22.7	16	34.8
SLIGHTLY WORSE	6	14.3	0	0	3	6.5
VERY MUCH IMPROVED	2	4.8	13	29.5	9	19.6
VERY MUCH WORSE	1	2.4	0		0	0
Total	42		44		46	

Percent of Therapeutic Response is a secondary efficacy variable for Study 97-M-02. The definition of *Therapeutic Response* is given in Section 2. Numbers of Therapeutic Responses by treatment are shown in Table 5.1.4 below. The chi-square indicates a significant association between treatments and response (p-value = 0.001).

Table 5.1.5
Secondary efficacy measure – Percent of Therapeutic Response
Study 97-M-02

Treatment	No Response	Response	Total
Placebo	34	8	42
d-**MPH**, 2.5-10mg	15	29	44
dl-**MPH**, 5-20mg	25	21	46
Total	74	58	132

Subgroup analyses (Study 97-M-02)

As approximately over 80% of the subjects are Caucasian, sub-group analysis by race is not done. The Kruskal-Wallis test applied to the data on the primary efficacy measure for the sub-group of female subjects indicates that there is no significant difference among the three treatment groups (p-value = 0.293).

Study 97-M-02 included 39 (out of 119) adolescents (12-19, inclusive). The Kruskal-Wallis test applied to the data on the primary efficacy measure for this subgroup of adolescent subjects indicated that there is no significant difference among the three treatment groups (p-value = 0.7157).

5.2 Study 97-M-03

The protocol defined primary efficacy measure for this study is the percent of treatment failure. The Mantel-Haenszel test is the protocol defined primary method of data analysis. As mentioned in Section 3 the definition of percent treatment failure is based on Clinical Global Impression-Improvement. A summary of CGI-I is shown below.

Table 5.2.1
Final Clinical Global Impression-Improvement (CGI_I) Assessment
Study 97-M-03 (LOCF)

CGI_I	**Placebo**		***d*-MPH**	
	Frequency	Percentage	Frequency	Percentage
MINIMALLY IMPROVED	2	5.0	2	5.7
MUCH IMPROVED	1	2.5	5	14.3
MUCH WORSE	16	40.0	5	14.3
NO CHANGE	7	17.5	10	28.6
SLIGHTLY WORSE	4	10.0	10	28.6
VERY MUCH IMPROVED	1	2.5	2	5.7
VERY MUCH WORSE	9	22.5	1	2.9
	40		35	

Treatment-wise percent treatment failures for Study 97-M-03 are presented in Table 5.2.2 below.

Table 5.2.2
Primary efficacy measure – Percent of Treatment Failure
Study 97-M-03 (LOCF)

Treatment	Not Failure	Failure	Total
Placebo	15	25	40
***d*-MPH**	29	6	35
Total	44	31	75

The percentages of treatment failures under placebo and the test drug are 62% and 17%, respectively. The chi-squared test indicates that these proportions of failures are significantly different (p-value = 0.001). All three test statistics under CMH PROCedure are observed to be 15.82 with p-value = 0.001.

As the LOCF data contain only one dropped out observations, OC analysis is not shown here.

Secondary Efficacy Measure: The Teacher SNAP-ADHD Change from Baseline is a secondary efficacy variable for Study 97-M-03. Descriptive statistics are shown in Table 5.2.3 below.

Table 5.2.3
Summary Statistics for Teacher SNAP-ADHD and Change from Baseline

	Baseline				
Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	35	0.7357	0.685		
d-MPH, same dose	28	0.6553	0.691		
	Final Visit				
Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	38	1.454	0.885		
d-MPH, same dose	32	0.712	0.654		
	Teacher SNAP Change from Baseline				
Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	34	0.716	0.821		
d-MPH, same dose	26	0.012	0.648		

One-way analysis of variance indicates that the two treatment groups are significantly different with respect to the change in Teacher SNAP-ADHD scores (p-value = 0.0007). The Teacher SNAP-ADHD score change from Visit 8 to Visit 10 was significantly greater in the placebo group than in the d-MPH group indicating a worsening of symptoms.

Study 97-M-03: Observed Cases data analysis- Secondary efficacy
As per the data submitted on 3/8/01, a total of only 50 patients completed the study. The descriptive statistics on the primary efficacy variables are as follows.

Table 5.2.4
Change from baseline in the final visit Teacher SNAP-ADHD

Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	28	0.6536	0.7665		
d-MPH, same dose	22	0.0227	0.6775		

One way analysis of variance of observed cases data indicates that the treatment groups are significantly different (p-value = 0.0038) and the results are again in favor of *d*-MPH.

Subgroup analysis (Study 97-M-03)

As approximately over 80% of the subjects are Caucasian boys, sub-group analyses by gender and race is not done. There were only 20 adolescent subjects in Study 97-M-03. Sub-group analysis is not done as the chi-square test is not valid due to small cell values.

5. REVIEWER'S OVERALL CONCLUSIONS

- The Study 97-M-02 baseline data indicate that the treatment groups were not comparable with respect to the Teacher SNAP-ADHD rating scale.

- The **Study 97-M-02** data on the primary efficacy measure provide sufficient evidence to indicate that the change at the final visit Teacher SNAP-ADHD Rating scale from baseline under each of [redacted] group is significantly higher than that of under placebo. That is, each of [redacted] group is efficacious compared to placebo. These conclusions are supported by the data on Percent of Therapeutic Response, a secondary efficacy measure proposed in Study 97-M-02. However, as the Teacher SNAP-ADHD Rating score at the end of the treatment phase for *d,l*-MPH observed to be over 1, it might be stated that the behavior of children under *d,l*-MPH treatment group may not be well controlled.

- The **Study 97-M-03** data provide sufficient evidence to conclude that the Percent of Therapeutic Failures under *d*-MPH is significantly smaller than that of under placebo. Also, the data on the change in the final visit Teacher SNAP-ADHD Rating score from baseline support the claim that *d*-MPH is efficacious compared to placebo.

/S/

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STATISTICAL REVIEW AND EVALUATION
Review for Stability Data

NDA#:	21-278 (S024)
APPLICANT:	Celgene Corp
NAME OF DRUG:	d-*threo*-methylphenidate HCl
INDICATION:	ADHD
DATES OF DOCUMENTS:	12/28/00, 2/28/01, 3/15/01, 5/21/01, 5/29/01,6/18/01
CHEMISTRY REVIEWER:	Donald Klein, Ph.D. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen, Ph.D. (HFD-710)

I. Background

The sponsor submitted updated drug substance and drug product stability data in the Drug Substance and Drug Product Stability Update of CMC on December 28, 2000. Stability data were then reported for four pilot scale lots (Lot 120297-C, Lot 619-70-622, Lot 619-71-599 and Lot 619-71-694) of d-*threo*-methylphenidate (d-MPH) HCl drug substance stored for at least 12 months at [redacted] and 6 months at [redacted] Twelve months of stability data at [redacted] and as well as 6 months of stability data at [redacted] were also reported for d-MPH drug products (2.5 mg, 5 mg and 10 mg tablets). On May 21, 2001, the sponsor sent an amendment for providing 6 more months of data for the d-MPH drug product at [redacted] For drug substance or drug product, 24 months of retest period or expiration dating period were requested, respectively, at ambient room temperature conditions.

This review does not address any findings made at CMC inspections of the various sites.

[redacted] no longer makes the drug product. However, almost all stability data are based on [redacted] lots. These will be analyzed in this review. The new manufacturer of the drug product is [redacted] However, there are only few months of stability data available from this site, which are too few to be analyzed alone at this point and which should not be grouped with the [redacted] data. The [redacted] data should be analyzed when there are at least one year of stability data available. The detailed information about each d-MPH lot studied in the stability trials and the status of the stability trials are summarized in Tables 1 and 2. Note that, during the course of d-MPH process development and scale up, the synthesis was modified slightly to accommodate variations in processing equipment and parameters between different manufacturing sites. Celgene has tracked the three different synthetic processes used during development and has named them Routes [redacted] For example, [redacted] It was also noticed that the drug products (2.5 mg, 5 mg, and 10 mg tablets) in this stability analysis were made from the drug substance lots 619-70-622 and 619-71-599 only.

Table1: Summary of d-*threo*-Methylphenidate HCl Drug Substance Stability Data

Lot Number	Site of Manufacture	Process Route (Scale)	Stability Storage and Testing Site	Packaging Configuration	Data Status for
120297-C	Celgene				
619-70-622					
619-71-599					
619-71-694					

Table 2: Drug Product Batch History for Primary Stability Studies

Dosage Strength	Batch Number	Nominal Batch Size (Number of Tablets)	D-MPH Drug Substance Lot Number
2.5 mg	039718		619-70-622
2.5 mg	039719		619-70-622
2.5 mg	039720		619-71-599
5 mg	128693		619-70-622
5 mg	039721		619-70-622
5 mg	039722		619-71-599
10 mg	039723		619-70-622
10 mg	039724		619-70-622
10 mg	039725		619-70-599

II. Sponsor's Stability Data Analyses and Conclusions

For Drug Substance:

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IV. Summary

Since 17 months of retest period (RP) were shown for d-*threo*-Methylphenidate Hydrochloride (d-MPH) HCI drug substance using the proper statistical model (by packaging), the sponsor's requested 24 months of retest period were clearly not supported by the data.

There are [redacted] months of estimated expiry period (EEP) shown for the drug product stored at long-term [redacted] condition. There were only [redacted] months of EEP shown for the 2.5 mg tablet and [redacted] months of EEP shown for the 5.0 mg tablet stored at the intermediate [redacted] condition. Since the labeled controlled room temperature condition will be [redacted] the sponsor's requested [redacted] months of expiration dating period was not strongly supported by the data.

There are only 12 months of data provided for the above 17 months RP (drug substance) and [redacted] months of EEP (drug product). It is suggested to re-analyze these data at future time points.

Some data inconsistency was noticed in the sponsor's May submission. However, the conclusions were not affected.

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